(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 October 2001 (18.10.2001)

PCT

(10) International Publication Number
WO 01/077167 A3

(51) International Patent Classification[7]: C07K 14/47, A61K 48/00, A61P 25/28

(21) International Application Number: PCT/US01/11043

(22) International Filing Date: 5 April 2001 (05.04.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/194,684 5 April 2000 (05.04.2000) US

(71) Applicant *(for all designated States except US)*: **UNIVERSITY OF TENNESSEE RESEARCH CORPORATION** [US/US]; Suite 403, 1534 White Avenue, Knoxville, TN 37996-1527 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SOLOMON, Alan** [US/US]; Suite 403, 1534 White Avenue, Knoxville, TN 37996-1527 (US). **WALL, Jonathan** [GB/US]; Suite 403, 1534 White Avenue, Knoxville, TN 37996-1527 (US). **HRNCIC, Rudi** [BA/US]; Suite 403, 1534 White Avenue, Knoxville, TN 37996-1527 (US). **SCHELL, Maria** [US/US]; Suite 403, 1534 White Avenue, Knoxville, TN 37996-1527 (US).

(74) Agents: **TUSCAN, Michael, S.** et al.; Morgan, Lewis & Bockius LLP, 1111 Pennsylvania Avenue, NW, Washington, DC 20004 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
28 August 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/077167 A3

(54) Title: METHODS OF INVESTIGATING, DIAGNOSING, AND TREATING AMYLOIDOSIS

(57) Abstract: The present invention provides a therapeutic method for removing amyloid fibrils from a patient by administering an effective amount of amyloid fibril to generate an immune response. The present invention also provides a transgenic animal that develops systemic AA amyloidosis within three weeks for use as a tool to investigate AA amyloidosis and to evaluate agents that may be potentially useful in preventing and treating amyloid-related disorders. Further, the present invention provides diagnostic assays for monitoring immunoglobulin light chain fibrillogenesis in real-time and for identification of the chemical nature of the protein in amyloid deposits which enables the determination of the type of amyloidosis for therapeutic and prognostic purposes.

INTERNATIONAL SEARCH REPORT

Int nal Application No
PCT/US 01/11043

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K14/47 A61K48/00 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 00 72876 A (NEURALAB LIMITED) 7 December 2000 (2000-12-07) claims 1-57 ---	1-3
X,P	HELMUTH ET AL: "Further progress on a beta -amyloid vaccine" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, US, vol. 289, no. 5478, 21 July 2000 (2000-07-21), pages 349-496, XP002154517 ISSN: 0036-8075 the whole document ---	1-3
X	WO 99 27944 A (ATHENA NEUROSCIENCES INC.) 10 June 1999 (1999-06-10) claims 1-66 --- -/--	1-3

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 September 2002	06 12. 2002
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Siatou, E

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/US 01/11043

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 31996 A (MILKHAUS LABORATORY) 30 November 1995 (1995-11-30) claims 1-19 ---	1-3
X	WO 95 12815 A (THE RESEARCH FOUNDATION OF STATE UNIVERSITY OF NEW YORK) 11 May 1995 (1995-05-11) claims 1-22 ---	1-3
X	WO 91 16819 A (MOLECULAR RX. INC.) 14 November 1991 (1991-11-14) claims 1-11 ---	1-3
X	SCHENK D ET AL: "Immunization with amyloid-beta attenuates Alzheimer -disease-like pathology in the PDAPP mouse [see comments]" NATURE, MACMILLAN JOURNALS LTD. LONDON, GB, vol. 400, no. 6740, 8 July 1999 (1999-07-08), pages 173-177, XP002154168 ISSN: 0028-0836 the whole document -----	1-3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/11043

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-2 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-3

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-3 relate to an extremely large number of possible compositions and methods. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/products/apparatus/methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compositions and methods where the amyloid fibril is selected from the compounds listed in page 22, lines 21-24.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-3

   Method and composition for removing amyloid deposits by administering an effective amount of amyloid fibril to a patient

2. Claims: 4-27, 31-32

   Method for identifying agents effective in preventing/treating amyloidosis or increasing rate of development of amyloid deposits in a transgenic animal carrying an IL-6 gene and transgenic animals carrying an IL-6 gene.

3. Claims: 28-29

   Method for identifying agent which inhibit fibrilogeneis or are fibrilogenic by incubating with thioflavin T (ThT) and measuring fluorescence intensity

4. Claim : 30

   Method for identifying the chemical nature of proteins in amyloid deposits

INTERNATIONAL SEARCH REPORT

Information on patent family members

In ...nal Application No
PCT/US 01/11043

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0072876 A	07-12-2000	AU 5316300 A	18-12-2000
		BG 106140 A	30-08-2002
		BR 0011103 A	19-03-2002
		CN 1377278 T	30-10-2002
		EP 1185296 A2	13-03-2002
		HU 0201205 A2	28-08-2002
		NO 20015758 A	30-01-2002
		SK 17182001 A3	10-09-2002
		TR 200103469 T2	21-05-2002
		WO 0072876 A2	07-12-2000
WO 9927944 A	10-06-1999	BG 104562 A	31-01-2001
		BR 9815357 A	24-10-2000
		CA 2312920 A1	10-06-1999
		CN 1281366 T	24-01-2001
		DE 1033996 T1	07-06-2001
		EE 200000379 A	16-04-2001
		EP 1033996 A1	13-09-2000
		HR 20000443 A1	31-10-2000
		HU 0100627 A2	28-06-2001
		JP 2002502802 T	29-01-2002
		NO 20002784 A	31-07-2000
		PL 342649 A1	18-06-2001
		TR 200001608 T2	23-07-2001
		WO 9927944 A1	10-06-1999
		AU 1706199 A	16-06-1999
		ZA 9810932 A	02-07-1999
WO 9531996 A	30-11-1995	AT 202940 T	15-07-2001
		AU 686818 B2	12-02-1998
		AU 2651995 A	18-12-1995
		CA 2191101 A1	30-11-1995
		DE 69521700 D1	16-08-2001
		DE 69521700 T2	25-10-2001
		EP 0760676 A1	12-03-1997
		JP 3064013 B2	12-07-2000
		JP 9510732 T	28-10-1997
		US 5851996 A	22-12-1998
		US 6174916 B1	16-01-2001
		WO 9531996 A1	30-11-1995
		US 5753624 A	19-05-1998
WO 9512815 A	11-05-1995	US 5744368 A	28-04-1998
		AU 8131094 A	23-05-1995
		WO 9512815 A1	11-05-1995
WO 9116819 A	14-11-1991	AT 153534 T	15-06-1997
		CA 2081482 A1	28-10-1991
		DE 69126304 D1	03-07-1997
		DE 69126304 T2	04-09-1997
		EP 0526511 A1	10-02-1993
		JP 2980677 B2	22-11-1999
		JP 6502387 T	17-03-1994
		US 5851996 A	22-12-1998
		US 6174916 B1	16-01-2001
		WO 9116819 A1	14-11-1991
		US 5753624 A	19-05-1998